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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/896,692	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-4-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 8-6-04.

Claims 1-12 and 14-41 are pending in the instant application.

The allowability of claims 16-22, 29 and 30 in the Office action mailed 5-5-04 is hereby withdrawn in light of the rejections set forth below.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to methods and compositions comprising oligonucleotides "having a nucleotide sequence consisting of 21 nucleotides of the sequence set forth as SEQ ID NO: 5" (e.g. see lines 1-2 of claim 1; lines 4-5 of claim 16). It is unclear whether the claims are drawn to oligonucleotides consisting of 21 nucleotides, or whether they are drawn to oligonucleotides comprising nucleotides consisting of 21 nucleotides (e.g.

of lengths exceeding that set forth in SEQ ID NO: 5. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-41 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting HIV-1 or HIV-2 infection in an isolated cell in vitro, and for a method of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a human comprising the intravenous administration of an oligonucleotide consisting of SEQ ID NO: 1, 2, 3, 4 or 5, does not reasonably provide enablement for methods of inhibiting HIV-1 or HIV-2 infection in cells in vivo comprising the administration of these antisense, or for methods of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a mammal comprising the administration of an oligonucleotide comprising SEQ ID NO: 1, 2, 3, 4 or 5, nor for methods of introducing an intact oligonucleotide into a mammal comprising oral administration of unmodified antisense oligonucleotides, whereby the oligonucleotides are present in intact form in the systemic plasma following oral administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting HIV-1 or HIV-2 infection in cells in vitro and in vivo, and methods of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a mammal comprising the administration of an oligonucleotide comprising SEQ ID NO: 1, 2, 3, 4 or 5, as well as being drawn to methods of introducing an intact oligonucleotide into a mammal comprising oral administration of unmodified antisense oligonucleotides, whereby the oligonucleotide is present in intact form in the systemic plasma following oral administration.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23: 45-50, *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more

sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide. (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the important and inordinately difficult challenge of the delivery of therapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided adequate guidance in the specification toward a method of inhibiting HIV-1 or HIV-2 infection of target cells in vivo comprising administration of antisense, nor of treating HIV-1 or HIV-2 infection in any mammal comprising the administration of an oligonucleotide comprising SEQ ID NO: 1, 2, 3, 4 or 5, nor of introducing an intact oligonucleotide into a mammal comprising oral administration of unmodified antisense oligonucleotides, whereby the oligonucleotides are present in intact form in the systemic plasma following oral

administration. The specification teaches methods of inhibiting HIV-1 or HIV-2 infection in an isolated cell in vitro comprising the administration of antisense oligonucleotides consisting of SEQ ID NO: 1, 2, 3, 4 or 5 and methods of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a human comprising the intravenous administration of an oligonucleotide consisting of SEQ ID NO: 1, 2, 3, 4 or 5. One skilled in the art would not accept on its face these examples given of the in vitro inhibition of HIV infection of target cells, or the in vivo treatment of HIV-1 or HIV-2 in humans following the intravenous administration of oligonucleotides consisting of SEQ ID NO: 1, 2, 3, 4 or 5 as being correlative or representative of the ability to inhibit HIV infection in target cells in vivo comprising the administration of antisense, or of the ability to treat any mammal for HIV-1 or HIV-2 comprising the administration of antisense comprising SEQ. ID NO: 1, 2, 3, 4 or 5, or of the ability to introduce an intact oligonucleotide into a mammal comprising oral administration of unmodified antisense oligonucleotides, whereby the oligonucleotides are present in intact form in the systemic plasma following oral administration.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods of inhibiting HIV-1 or HIV-2 infection in cells in vitro and in a mammal, and methods of exhibiting antiviral activity or treating HIV-1 or HIV-2 infection in a mammal comprising the administration of an oligonucleotide comprising SEQ ID NO: 1, 2, 3, 4 or 5, as well as being drawn to methods of introducing an intact oligonucleotide into a mammal comprising oral

administration of unmodified antisense oligonucleotides, whereby the oligonucleotide is present in intact form in the systemic plasma following oral administration.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues with antisense oligonucleotides comprising SEQ ID NO: 1, 2, 3, 4 or 5, whereby infection of target cells with HIV-1 or HIV-2 is inhibited, or whereby treatment effects are provided in any mammal comprising the administration (including oral administration) of antisense comprising SEQ ID NO: 1, 2, 3, 4 or 5, or whereby intact oligonucleotides are present in the plasma following oral administration of unmodified oligonucleotides. Since the specification fails to provide any particular guidance for inhibiting HIV-1 or HIV-2 infection in target cells in an organism comprising the administration (e.g. by any route) of antisense, or for treating HIV-1 or HIV-2 infections in any mammal comprising the administration of antisense oligonucleotides comprising SEQ ID NO: 1, 2, 3, 4 or 5, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

In light of the ambiguous language of claim 1 with respect to whether the claims are drawn to compositions comprising oligonucleotides comprising a nucleotide sequence consisting of 21 nucleotides (e.g. more than 21 nucleotides), or compositions comprising oligonucleotides consisting of a nucleotide sequence of 21 nucleotides (e.g.

not more than 21 nucleotides), (see the 112, second rejection above) in applying art the claims are interpreted as being drawn to compositions comprising oligonucleotides comprising a nucleotide sequence consisting of 21 nucleotides (e.g. more than 21 nucleotides).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 14, 15 are rejected under 35 U.S.C. 102(a) or 102(e) as being anticipated by Cohen et al.

Cohen et al teach a 21 nucleobase synthetic oligonucleotide that is specifically complementary to nucleotides 324-345 of a conserved gag region of the HIV1 genome, and which comprises phosphorothioate internucleotide linkages, and which oligonucleotide inhibits HIV-1 or HIV-2 infection in a cell in vitro or exhibits antiviral

activity against HIV-1 or HIV-2 (See SEQ ID NO: 7 of Cohen et al. See also col. 1-2 of Cohen et al).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 14, 15 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al as applied to claims 1, 14 and 15 above, and further in view of Baracchini et al.

The claims are drawn to a 21 nucleobase synthetic oligonucleotide that is specifically complementary to nucleotides 324-345 of a conserved gag region of the HIV1 genome, and pharmaceutical formulations thereof, which oligonucleotide comprises phosphorothioate internucleotide linkages, at least four 5' or 3' terminal ribonucleotides which flank deoxynucleotides, and which terminal ribonucleotides comprise 2'-O-methyl ribonucleotides.

Cohen et al is relied upon as cited in the 102 rejection above.

Cohen et al do not teach oligonucleotides further comprising at least four 5' or 3' terminal ribonucleotides which flank deoxynucleotides, and which terminal ribonucleotides comprise 2'-O-methyl ribonucleotides.

Baracchini et al teach antisense oligonucleotides comprising 5' and/or 3' terminal ribonucleotides, which ribonucleotides comprise 2'-O-methyl groups (See col. 6-7).

It would have been obvious to one of ordinary skill in the art to incorporate phosphorothioate internucleotide linkages, as well as terminal, 2'-O-methyl modified ribonucleotides into antisense oligonucleotides because Baracchini et al teach the incorporation of both phosphorothioate modifications and modified ribonucleotides into antisense oligonucleotides for enhancing oligonucleotide stability from exonucleases and enhancing target cell uptake of antisense. One of ordinary skill in the art would have been motivated to incorporate 2'-O-methyl modified ribonucleotides into the terminal positions of antisense oligonucleotides in order to enhance oligonucleotide stability, and one of ordinary skill in the art would have expected that such modified terminal ribonucleotides would enhance antisense stability and metabolic halflife, thereby making more antisense available for target gene binding. One of ordinary skill in the art would have been motivated to incorporate multiple (e.g. 1-4 residues) modified ribonucleotides into the 5' and/or 3'-terminal regions of the antisense oligonucleotides because these modifications have been taught to enhance stability of the antisense, and one of ordinary skill in the art would have expected that stability would be enhanced with increasing numbers of modified residues inserted onto the 5' and/or 3' termini.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments and Amendments

Applicants' arguments filed 2-4-04 have been considered but they are not found fully persuasive. Applicants argue that the claimed invention is neither overly broad in scope nor requires undue experimentation. Applicants argue that the invention is enabled for inhibiting HIV-1 and HIV-2 infection in target cells in a mammal because the instant disclosure teaches the inhibition of infection in MT-4 cells in vitro using SEQ ID NO: 1. Contrary to Applicants' assertions, the ability to inhibit infection in vitro is not representative of the ability to inhibit infection in vivo. The ability to target isolated cells in culture with an antisense at an optimal concentration is not necessarily correlative of the conditions or concentrations required or obtainable in vivo, whereby infection of HIV-1 or –2 is inhibited. Applicants have shown treatment of HIV-1 infections in humans in vivo comprising administration of antisense consisting of SEQ ID NO: 1. This is enabling for treatment of HIV-1 or HIV-2 infections in vivo via iv administration of the 21-mer (or 22-mer) oligonucleotides consisting of SEQ ID NO. 1, 2, 3, 4 or 5, but not of the ability to inhibit infection in vivo. Reducing viral load is not analogous to, or necessarily representative of the ability to inhibit HIV infection of target cells. And, contrary to Applicants' assertions, it would require undue experimentation beyond that taught in the instant disclosure to inhibit infection of target cells in a mammal in vivo using the antisense claimed.

Applicants argue that the target accessibility problem has been overcome for the full breadth of the claimed invention because of the treatment efficacy shown in vivo using SEQ ID

NO: 1. Applicants are correct that the target accessibility problem has been overcome for the scope drawn to treating HIV infections, but not of inhibiting HIV infections in cells in a mammal. As stated above, the MT-4 in vitro cellular data illustrating inhibition of HIV infection is not representative of in vivo inhibition of infection.

Applicants also argue that the reasoning for the rejection is inconsistent because failure of one antisense (e.g directed to a different target gene), or the illustration in the art of an isolated statistical failure in a phase III clinical trial required for FDA approval, for instance, do not negate the patentability of the instant invention. Contrary to Applicants' assertions, and as illustrated above in the teachings of Crooke, Branch, Agrawal, Chirilla and Peracchi, antisense therapy is currently a highly unpredictable field, and the success of one antisense in vivo cannot be extrapolated to another antisense. The ability of an antisense to reach and inhibit its appropriate target gene, which is harbored in an appropriate target cell in vivo, must be determined empirically for that antisense, for that target gene and for that method claimed (e.g. inhibition of viral infectivity), thus requiring undue experimentation. And so this is the case for antisense targeting HIV sequences, and further whereby HIV infections are inhibited in appropriate target cells in vivo in a mammal.

Applicants argue that the specification also provides general teachings in the field of antisense therapy, including examples of in vivo testing methods that are to be employed for testing antisense efficacy. Methods of evaluating the presence of intact antisense after oral administration, for instance, have been demonstrated in the instant disclosure. Applicants are correct that these methods have been disclosed in the instant application. But, contrary to Applicants' assertions, the ability of antisense oligonucleotides that comprise 5' and 3' terminal 2'-O modifications to remain intact is neither representative of the ability of unmodified antisense oligonucleotides to remain intact, nor is it representative of the ability of modified or unmodified

antisense to inhibit infections in a mammal. For these reasons, the claimed invention is rejected for lacking enablement over the scope claimed.

Applicants argue that Cohen does not anticipate the instant invention because the reference does not provide an enabling disclosure of the instant claimed invention and instead teaches methods of separating modified and unmodified oligonucleotide analogs. Applicants are correct that Cohen teaches methods of separating modified and unmodified oligonucleotide analogs, but contrary to Applicants' assertions, the compound taught by Cohen is the same compound claimed and as such imparts the same properties of the claimed compound. Cohen has not been cited as anticipating any methods and thus properly anticipates the instantly claimed compound.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
10-13-04

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